Thalidomide Pharmion

Information Brochure

PHARMION

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Information Brochure

Thalidomide Pharmion 50 mg Hard Capsules are approved for use in Australia for:

(i) the treatment of multiple myeloma after failure of standard therapies

(ii) the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). Thalidomide is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

This monograph has been produced to provide physicians with detailed information on the product. However, physicians are strongly advised to carefully consult the Product Information before prescribing Thalidomide Pharmion 50 mg Hard Capsules.

Prescribers are also reminded that this product is made available subject to a strict risk management programme involving education and managed distribution. This programme, the Pharmion Risk Management Programme (PRMP), which is described towards the end of this Monograph, requires the pre-registration of prescribing physicans, patients and dispensing pharmacies and their agreement to adhere to all the principles and processes of the programme.

Thalidomide Pharmion 50mg Hard Capsules®

(thalidomide)

Teratogenic effects

Thalidomide has caused severe birth defects when taken during pregnancy. Thalidomide should never be used by women who are pregnant or who could become pregnant whilst taking the drug or could become pregnant within 4 weeks after stopping the drug. Even a single dose can cause birth defects.

PBS Information: This product is not listed on the PBS.

Contents

Introduction

History of Thalidomide

Thalidomide was developed in the former West Germany in 1954 and marketed in the late 1950s and early 1960s in 46 countries worldwide, including the UK (where it was introduced in 1958).[1] Marketed initially as a sedative-hypnotic, thalidomide represented a 'safe' alternative to barbiturates for the treatment of insomnia. The usefulness of thalidomide as a treatment for morning sickness was, ironically, recognised shortly thereafter. The subsequent post-marketing epidemic of severe birth defects is infamous, and the drug was withdrawn from the world market by 1962.[2]

It is estimated that >10,000 infants were born with deformities that were directly attributable to maternal thalidomide usage.[1] Furthermore, the mortality rate of affected infants at, or shortly after, birth was ~40%. The major defects associated with thalidomide involve abnormalities of the extremities, including phocomelia, amelia, missing feet and hands, and absent or hypoplasic bones. Anotia, microtia, anophthalmos, microphthalmos, facial palsy, cleft lip or palate, abnormalities of the heart, kidneys, genitals, spinal cord, urinary and alimentary tracts, and neurodevelopmental problems (e.g. epilepsy, autism, mental handicap, dyslexia) have also been observed.

The foetus is most sensitive to the teratogenic effects of thalidomide 34 to 50 days after the beginning of the last menstrual period; however, birth abnormalities are possible at any stage of pregnancy and can be produced by a single dose of thalidomide.[3,4] Although the consequences of foetal thalidomide exposure have been known for over 40 years, the exact mechanism(s) underlying these harmful actions of thalidomide have not been identified.

Usefulness of Thalidomide

Despite thalidomide's notoriety in producing birth defects, the drug has proved useful for the treatment of many disease conditions. In the mid-1960s, Sheskin accidentally discovered that thalidomide improved the symptoms of erythema nodosum leprosum (ENL), an inflammatory complication of leprosy (Hansen's disease).[2] The immunomodulatory, anti-inflammatory and anti-angiogenic properties of thalidomide are presently being investigated in a number of clinical conditions including advanced multiple myeloma, Behçet's disease, HIV-associated oral ulceration and chronic graft-*versus*-host disease.[1,5]

Currently, thalidomide is indicated in the USA for the acute treatment of the cutaneous manifestations of moderate to severe ENL and for the treatment of ENL relapses in patients previously treated with thalidomide. However, thalidomide is also used on an investigational basis in cancer patients, particularly those with multiple myeloma. For example, 73% of thalidomide use (in 10,456 patients) during its first 18 months on the US market was for the treatment of cancer patients.[2]

Chemistry of Thalidomide

Physico-chemical Properties

Thalidomide is a white, virtually odourless, crystalline compound which is known chemically as 2-phthalimidoglutarimide. It is derived from a naturally occurring amino acid, glutamic acid. The thalidomide molecule consists of two amide rings – one is a phthalimide and the other is a glutarimide (Fig. 1). The currently available formulation of thalidomide is a racemic mixture consisting of two optical isomers – the R-isomer and the S-isomer. A racemic mixture is a combination of two isomers, or mirror image forms of a molecule, which have virtually identical chemical properties. The S-isomer (in contrast to the R-isomer) has been linked to thalidomide's teratogenic effects. However, attempts to formulate the R-isomer have not solved the problem of teratogenicity, as the two isomers are readily inter-convertible *in vivo*.

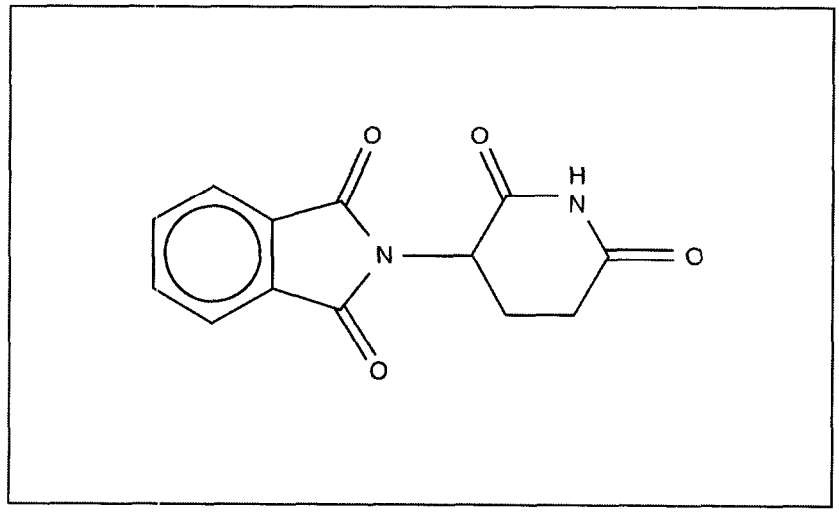

Figure 1 Structure of thalidomide

Clinical Pharmacology

Mechanism of Action

Thalidomide is an immunomodulatory agent with a broad spectrum of effects on immune function, cytokine secretion, angiogenesis, cell adhesion and cell proliferation.[6,7] However, it is presently unclear which of these effects account for its therapeutic activity.[8] At least two mechanisms, immune modulation and anti-angiogenesis, are believed to be important for the anti-tumour activity of thalidomide, and these in turn may be mediated through the drug's multiple actions on cellular cytokine secretion.

Inhibition of tumour necrosis factor-α (TNF-α) production

The most pronounced and best-described effect of thalidomide is that on TNF-α generation and release.[7] TNF-α is a cytokine that is involved in up-regulation of endothelial cell integrin expression, a process crucial for new blood vessel formation. Thalidomide decreases TNF-α production by accelerating the degradation of mRNA encoding the protein.[9] This mechanism differs from that proposed for pentoxifylline and corticosteroids, which suppress lipopolysaccharide (LPS)-induced TNF-α RNA transcription and translation, respectively.[9]

In vitro, thalidomide selectively inhibited human monocyte TNF-α production stimulated by LPS or mycobacterium-based agonists, other cytokines remaining unaffected.[10] TNF-α inhibition was concentration-dependent and occurred at thalidomide concentrations comparable to those achieved in humans with thalidomide doses of ≤400 mg/day. The degree of TNF-α inhibition *in vitro* was about 40% at the therapeutically achievable serum concentration of 1 pg/ml. Moreover, an *in vitro* study using alveolar macrophages from patients with tuberculosis or other diseases associated with macrophage activation demonstrated that thalidomide attenuated the LPS-stimulated increase in number of cells staining with antibodies to TNF-α.[11]

In patients with ENL, who show abnormally high serum levels of TNF-α, treatment with thalidomide 100–200 mg/day has been shown to reduce TNF-α levels coincident with alleviation of symptoms.[12] In patients co-infected with human immunodeficiency virus-1 (HIV-1) and *Mycobacterium tuberculosis* who were receiving antituberculosis treatment, thalidomide treatment caused a ≥10% reduction in plasma TNF-α levels, with the reduction being most pronounced in patients who had elevated baseline TNF-α levels.[13]

Immunomodulatory effects

Thalidomide has a wide range of stimulatory and inhibitory effects on the immune system: it inhibits leukocyte chemotaxis and phagocytosis; it reduces tumour-associated macrophage infiltration; it down-regulates selected cell surface adhesion molecules involved in leukocyte chemotaxis; it promotes the switch to a Th2 immune response; and it depresses helper T-cell production in favour of cytotoxic T-cell production.[6,14] In addition, thalidomide has variable effects on cellular cytokine secretion *in vitro* and *in vivo*: it stimulates interleukin-2 (IL-2) and IL-12 production in HIV-infected patients; it enhances IL-4 and IL-5 production; it inhibits secretion of IL-6 (a cytokine required for survival and proliferation of myeloma cells); it stimulates secretion of IL-12 (a potent inhibitor of angiogenesis); it suppresses interferon gamma (IFN-γ) production in macrophages but stimulates IFN-γ production in lipopolysaccharide (LPS)-stimulated polymorphonuclear cells; and it blocks TNF-α production in patients with ENL.[14]

In vitro, thalidomide reduces HIV-1 replication in peripheral blood mononuclear cells (PBMCs) from HIV-1-infected hosts and in agonist-stimulated latently infected cell lines.[15] Thalidomide-induced inhibition of viral activation in infected PBMCs may be expressed through the monocyte population, although this has not been conclusively demonstrated.[15]

In vivo, thalidomide modifies a number of integrin receptors, including β1-integrins, β2-integrins, and surface components such as the 'homing receptor' (CD44) and other surface receptors such as ICAM-1 and selectins.[16] CD45RO receptor densities on CD4 helper cells are greatly reduced, and thalidomide also strongly down-regulates CD11a, CD11b, and CD18 on leukocytes.[16]

Anti-angiogenic activity

Thalidomide inhibits angiogenesis in several experimental assay systems, including rat and human vascular endothelial cell cultures[17] and the rabbit corneal micropocket assay.[18,19] In the latter model, thalidomide 200 mg/kg inhibited the vascularisation induced by basic fibroblast growth factor (bFGF) in the rabbit cornea by 30–50%.[18] The mechanism of thalidomide's anti-angiogenic action is unknown. The drug inhibits secretion of bFGF, an angiogenic factor produced by human tumours, but has no effect on bFGF-induced proliferation of endothelial cells in culture.[18] Current studies are focused on identifying possible active thalidomide metabolites, since the anti-angiogenic effect of thalidomide is not only species-specific, but is observed only following systemic administration, suggesting the need for metabolic activation of the drug.[7]

Clinical Pharmacokinetics

Absorption

The absolute bioavailability of thalidomide following oral administration is difficult to determine because of its poor aqueous solubility. In healthy volunteers and patients with leprosy, the mean time to peak plasma concentrations (T_{max}) ranged from 2.9–5.7 hours after oral intake, indicating that thalidomide is slowly absorbed from the gastrointestinal tract (Table 1).[7] While the extent of systemic drug absorption (as measured by the area under the plasma concentration–time curve [AUC]) is proportional to dose over the range 200–1,200 mg given once or twice daily in healthy

Table 1. Pharmacokinetic parameters (mean % CV) for thalidomide following single oral dose administration (Celgene Corporation, data on file)

Dose	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg • h/ml)	T_{max} (h)	$T_{\frac{1}{2}}$ (h)
Healthy volunteers (n=14)				
50 mg	0.62 (52%)	4.9 (16%)	2.9 (66%)	5.5 (37%)
200 mg	1.76 (30%)	18.9 (17%)	3.5 (57%)	5.5 (25%)
400 mg	2.82 (28%)	36.4 (26%)	4.3 (37%)	7.3 (36%)
Patients with leprosy (n=6)				
400 mg	3.44 (53%)	46.4 (44%)	5.7 (27%)	6.9 (17%)

Abbreviations: CV = coefficient of variation; AUC = area under plasma concentration–time curve, C_{max} = peak plasma concentration; T_{max} = time to peak plasma concentration; $T_{\frac{1}{2}}$ = plasma elimination half-life.

volunteers, the peak plasma concentration (C_{max}) increases in a less than dose-proportional manner. This non-linear absorption and the observed prolongation of T_{max} at higher doses suggest that the poor aqueous solubility of thalidomide may limit its rate of absorption after oral intake.[7] Plasma concentration–time curves fit a one-compartment model with first-order absorption and elimination.[20] Co-administration of thalidomide with a high-fat meal causes minor (<10%) changes in its AUC and C_{max} values, but extension of T_{max} to ~6 hours.[21]

Distribution

The apparent volume of distribution for thalidomide in healthy volunteers is ~120 litres,[20] suggesting that the circulating drug is highly bound to plasma proteins. While administration of radiolabelled thalidomide to animals results in uniform tissue distribution of radioactivity, information on the distribution of thalidomide in humans is not available. Thalidomide and its metabolites have been identified in appreciable quantities in rabbit semen after oral administration.[22] Thalidomide has also been shown to be present in human semen after dosing.

Metabolism

The precise route of metabolism and the potential contribution of metabolites to the biological activity of thalidomide in humans remain uncertain. Although non-enzymatic hydrolysis and cytochrome P450-mediated hydroxylation have been proposed as the most likely metabolic pathways for thalidomide,[14] hepatic metabolism is reported to play only a very minor role in humans;[20] instead, it would appear that thalidomide is eliminated almost exclusively by spontaneous hydrolysis *in vivo*.[23] Thalidomide undergoes rapid non-enzymatic hydrolysis in aqueous solution at a pH of ≥6.0, forming 3 primary products: 4-phthalimidoglutaramic acid, 2-phthalimidoglutaramic acid and α-(O-carboxybenzamido) glutarimide.[24] After oral administration of thalidomide to humans, the metabolites 4-phthalimidoglutaramic acid and 3-hydroxyphthalimic acid are detectable in the urine.[14] Consistent with the claimed lack of involvement of the hepatic cytochrome P450 system in thalidomide's metabolism, the drug does not appear to induce or inhibit its own metabolism, since its pharmacokinetic profile after repeated dose administration to healthy volunteers for 21 days was essentially similar to the profile on the first day of dosing .[25] *In vitro* studies, however, indicate that hepatic microsomal biotransformation of the parent compound (possibly to an intermediary epoxide metabolite) is a prerequisite for the appearance of thalidomide's anti-angiogenic activity.[24]

Elimination

The mean plasma elimination half-life of thalidomide after single or repeated oral dose administration is ~5 to 7 hours,[7] and systemic clearance of the drug (~170 ml/min) is relatively slow.[20] The precise route of elimination of thalidomide in humans has yet to be established. However, renal clearance is low (1.15 ml/min), and only 0.7% of an orally administered dose of thalidomide is recovered in the urine as unchanged drug in the first 24 hours, suggesting a predominantly

non-renal route of elimination.[20] Although thalidomide is believed to be hydrolysed to a number of metabolites, only a minute fraction (0.02% of the administered dose) is recovered in the urine as 4-hydroxy-thalidomide over the period 12–24 hours post-dose.[7]

Special populations

HIV-positive patients

No significant pharmacokinetic differences have been noted between healthy human volunteers and HIV-positive patients following single-dose administration of thalidomide.[7]

Patients with leprosy

Preliminary findings suggest that patients with leprosy may have an increased bioavailability of thalidomide compared with healthy volunteers, but this remains to be confirmed.[7]

Renal or hepatic impairment

The pharmacokinetics of thalidomide in patients with renal dysfunction or hepatic impairment has not been determined.

Elderly

Comparison of pharmacokinetic data for thalidomide in healthy volunteers and leprosy patients ranging in age from 20 to 69 years does not reveal any age-related effect.[7] No pharmacokinetic data are available in children or adolescents <18 years of age.

Gender effects

There are no significant differences between the pharmacokinetics of thalidomide in men and women.[7]

Race effects

The effect of race on the pharmacokinetics of thalidomide has not been evaluated.

Erythema Nodosum Leprosum and the Role of Thalidomide

Erythema Nodosum Leprosum (ENL)

Epidemiology

Leprosy (Hansen's disease) is a chronic infectious disease caused by *Mycobacterium leprae*, a bacillus similar in structure to *Mycobacterium tuberculosis*, the causative agent of tuberculosis. The worldwide prevalence of leprosy at the beginning of 2002 was estimated by the World Health Organization (WHO) to be ~640,000 patients. Approximately 760,000 new cases were detected during 2001.[26]

Most cases of leprosy are concentrated in South-East Asia, the Americas and Africa, with India, Nepal, Brazil, Madagascar, Mozambique and Myanmar accounting for ~90% of the global leprosy total.[26] Leprosy affects individuals of all ages and both genders; however, in most geographic locations, males are affected more frequently than females, often by a ratio of 2 to 1. Leprosy is associated with poverty and rural residence.

ENL is a debilitating systemic inflammatory condition affecting up to 50% of lepromatous leprosy patients receiving anti-leprosy treatment. Although 15–25% of patients develop ENL during the first year of therapy, the disorder may not occur for up to 10 years post-treatment.[1]

Pathophysiology

The aetiology of ENL is not known; it may occur spontaneously, or may be caused by infection or stress, but it often develops in response to leprosy therapy. The most likely cause of the disorder is an immune reaction to deposits of *M. leprae* bacilli following their death. Other possible immunological triggers for ENL are complexes of *M. leprae* bacilli and anti-*M. leprae* antibodies.

ENL is associated with a local increase in cell-mediated immunity and is characterised by elevated levels of IL-2 and IFN-γ, increased numbers of helper T cells, and loss of suppressor T-cell activity.

Excessive macrophage production of cytokines, notably TNF-α, has also been implicated in the immunopathological consequences of ENL.

Clinical manifestations

ENL typically manifests as painful erythematous nodules of the skin and subcutaneous tissue, generally on the cooler areas of the body. The condition may be acute or chronic. In advanced conditions, pustules develop which may ulcerate, causing suppurative wounds and subsequent scarring. Patients may experience fever, anaemia, anorexia, weight loss, malaise, insomnia, leukocytosis, iritis, lymphadenopathy, acute epididoymo-orchitis, bone marrow suppression or liver inflammation.[27]

In later stages of the disorder, progressive neuritis may result in muscle atrophy and insensitivity, eventually leading to clawed hands and plantar ulcers that often necessitate amputation of distal extremities. Much of the morbidity and deformity of leprosy is due to ENL neuritis. Severe recurrent ENL can result in amyloidosis, which may lead to renal failure. In extreme cases, ENL may be fatal.

Histologically, ENL presents as acute vasculitis or panniculitis.

Treatment options for ENL

A number of treatment options for ENL have been tested, with mixed success.[28] Analgesics such as aspirin and paracetamol provide symptomatic treatment of pain and fever, but are of minimal benefit. Corticosteroids (e.g. prednisone, 30–60 mg daily) have proved to be effective in treating ENL, but relapse rates are high following discontinuation. Moreover, debilitating side effects usually appear with drugs of this class when given at high doses for prolonged periods of time.

High doses of the antibacterial drug clofazimine (200–300 mg daily) may be useful for the treatment of ENL, although its effect is modest and slow. The use of clofazimine at these doses is limited by

unacceptable side effects, such as skin pigmentation and occasionally fatal bowel obstruction. Clofazimine is often used as an adjunct to corticosteroid treatment.

As supported by a host of clinical evidence of its use in ENL, thalidomide is the most well-tolerated and efficacious treatment for this condition.

Clinical Efficacy of Thalidomide in ENL

The primary data demonstrating the effectiveness of thalidomide in ENL are extensive – the published medical literature describes the treatment of >6,000 patients over a 30-year period. These data include 1,848 patients examined in 6 controlled clinical trials, 29 open-label clinical trials and 15 case reports, and ~1,400 ENL patients treated on an investigational basis. Some of the key studies are described below.

Thalidomide versus *placebo*

The principal trial demonstrating the efficacy of thalidomide was reported by Sheskin & Convit.[27]

Study details

- Double-blind, randomised, placebo-controlled
- 52 lepromatous leprosy patients with ENL (37 males, 15 females; aged 17 to 58 years)
- Thalidomide (100 mg) or placebo was given four times daily for 7 days (dosage was reduced in patients <50 kg)
- Inclusion criteria: (1) clearly demonstrable erythema nodosum-like or erythema multiforme-like lesions, reactivation of old lesions, acute neuritis, acute iritis, acute iridocyclitis or acute orchitis, and (2) some of: pyrexia, adenopathy, arthralgia, myalgia, bone or abdominal pains, nephritis, rhinitis, insomnia, hepatosplenomegaly, epistaxis, anorexia or vomiting

- All patients were positive in bacteriological tests
- Leprosy duration was 8 months to 36 years; ENL duration was 3 months to 9 years
- Except for those patients on sulphone therapy, which was continued throughout the study, patients were not permitted any other medication
- ENL reactions were classified as severe, intermediate or mild/absent
- Primary endpoints: improvement in classification of overall ENL reaction severity (rated as complete (100%), striking (~50%), partial (~25%), none, or deterioration)
- Up to 4 treatment regimens were given to each patient (total regimens 173: thalidomide 85, placebo 88)

Main results

Evaluation of the overall severity of ENL reactions showed that improvement (complete, striking or partial) was seen in 92% of thalidomide regimens, compared with 27% for placebo ($p<0.001$). Of those regimens that resulted in no change, 86% were placebo; no cases of deterioration with thalidomide were recorded. A summary of these findings is presented in Table 2.

Table 2. Change in overall ENL reaction severity in response to thalidomide or placebo treatment regimens

ENL classification	Thalidomide*	Placebo*
Complete improvement	43 (50.5%)	4 (4.5%)
Striking improvement	13 (15.3%)	4 (4.5%)
Partial improvement	22 (25.9%)	16 (18.2%)
No change	7 (8.2%)	44 (50.0%)
Deterioration	0 (0%)	20 (22.8%)

*Expressed as number of treatment regimens (thalidomide = 85; placebo = 88) with percentage of total treatment regimens in parentheses.

When the severity of individual ENL reactions was assessed, improvements were seen following more treatment regimens with thalidomide than placebo. This finding was noted for lesions (94% *vs* 18% treatment regimens), neuritis or polyneuritis (89% *vs* 28%), arthralgia (90% *vs* 26%), headaches (92% *vs* 31%), insomnia (91% *vs* 37%), anorexia (88% *vs* 6%) and general condition (92% *vs* 20%).

Thalidomide improved the symptoms of ENL after 8 to 48 hours. Histopathologically, only thalidomide caused regression of the inflammatory infiltrate of reactive lesions, but not of the lepromatous component itself.

Side effects were minimal during the 7-day treatment course and did not affect patient compliance. With the exception of drowsiness, dizziness and nausea (more common with thalidomide), other adverse events, e.g. dry mouth, constipation and diarrhoea, were reported for both the drug and placebo group.

Thalidomide versus *aspirin*

Convincing evidence that thalidomide is superior to aspirin for ENL therapy was demonstrated in a study co-ordinated by the WHO in the early 1970s.[29]

Study details

- Multi-centre, double-blind, randomised, controlled
- 92 male ENL patients
- Thalidomide (100 mg) or aspirin (400 mg) was given four times daily for 7 days (dosage was reduced in patients <50 kg)
- Inclusion criteria: clearly demonstrable erythema nodosum-like or erythema multiforme-like lesions; patients with neuritis,

neuropathy, sub-febrile temperatures, with or without moderate pain, but not those with noticeably poor health, were included

- Patients were not permitted any other medication
- Primary endpoints: improvement in lepra lesions, fever and other lepra manifestations at 48 hours, 96 hours or 8 days after initiation of treatment
- A maximum of two 7-day regimens of each treatment were permitted for each patient (total regimens 214: thalidomide 116; aspirin 98)

Main results

Of all lesion sites examined, the effectiveness of thalidomide over aspirin was greatest with respect to cutaneous lesions (Fig. 2).

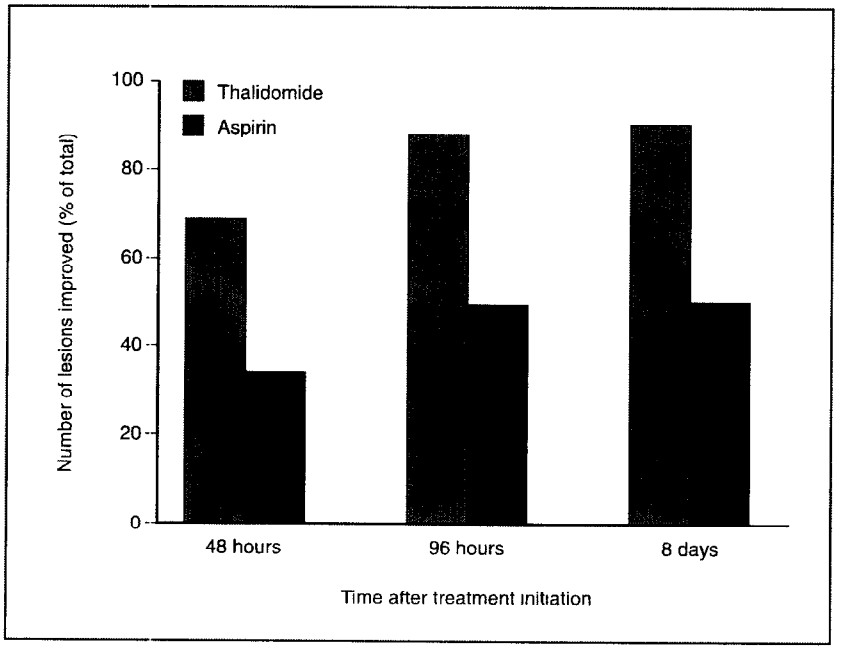

Figure 2. Improvement of erythema nodosum leprosum (ENL) skin lesions with thalidomide and aspirin when assessed at different time points after start of therapy

With respect to other lepra manifestations, fever (body temperature reduction to <38.5°C) was managed considerably better with thalidomide (n=42/44 reactions) than with aspirin (n=12/24 reactions) by day 8. Thalidomide was better than aspirin at reducing blood pressure, heart rate and leukocyte count.

Generally, many of the improvements seen with thalidomide were rapid, occurring within 48 hours of initiating treatment. Patients taking thalidomide were less likely to relapse than those receiving aspirin (48% *vs* 79% relapse rate).

Similar numbers of side effects occurred in both the thalidomide and aspirin treatment groups. Only leucopenia was more common with thalidomide (seen in 14% of the reactions) than with placebo (2%).

Thalidomide versus *placebo in steroid-dependent ENL*

The efficacy of thalidomide has also been demonstrated in two trials involving ENL patients receiving concurrent corticosteroid therapy.[30]

Study details

- Double-blind, randomised, placebo-controlled, cross-over design
- Ten male hospitalised steroid-dependent ENL patients: nine on prednisolone (average daily dose 28 mg); one on corticotrophin (average daily dose 20 IU); average therapy duration was 12 months (range 1 to 23 months)
- Thalidomide (100 mg) or placebo given three times daily; patients were also standardised on 100 mg dapsone twice weekly
- Inclusion criteria: lepromatous patients with histologically confirmed moderately severe or severe chronic ENL

- Lepra reaction duration before treatment: 9 months to 3.5 years
- Primary endpoint: reduction in total weekly steroid dosage (in response to symptomatic improvements)
- Both trials consisted of a no treatment period, a treatment 1 period, a treatment 2 period and a final no treatment period; period durations were either 4 weeks (trial 1) or 6 weeks (trial 2)

Main results

In trial 1, a favourable response (i.e. reduction in steroid dosage) was seen only with thalidomide (n=7/9 treatments, compared with n=0/9 for placebo). In trial 2, thalidomide (n=8/8 treatments) was similarly more effective than placebo (n=1/8 treatments). Most patients receiving thalidomide, but not placebo, relapsed after treatment was discontinued, as judged by an increased steroid requirement.

Striking improvements in cutaneous symptoms were associated with decreased steroid requirements. Skin lesion and fever responses to thalidomide were usually seen within days, with full resolution of lepra reaction symptoms observed after 1 to 2 weeks.

The results show that the need for corticosteroids may be reduced or eliminated in ENL patients receiving thalidomide. Therefore, when ENL is complicated with neuritis, concomitant use of steroids and thalidomide is indicated until the neuritis has resolved.

Long-term retrospective analysis of thalidomide use

Thalidomide has been used in the USA since 1975 on an investigational basis conducted under the US Public Health Service IND 11,359 (Celgene Corporation, data on file). The monitoring programme describes the clinical experience of ENL patients evaluated from 1978 to 1994 (representing 4,799 patient-years of data).

Study details

- Patients treated with thalidomide were evaluated annually by their physician, who recorded demographic and dosing information and rated the patient's response to treatment
- 1,368 patients in total (78.0% male, 22.0% female)
- 89% of patients were between 18 and 74 years of age
- Patients were classified as Hispanic (46.2%), Asian (36.7%), Caucasian (11.8%), black (3.8%) or other (1.5%)
- Patients were either lepromatous (84.5%) or borderline lepromatous (15.5%)
- Response categories included: good (complete ENL control), fair (partial ENL control), poor (no response), unknown response, and lost to follow-up

Main results

Of those patients with a response determination during year 1 of treatment (n=1,334), 80% showed complete control of ENL symptoms; only 2% showed no response. Most patients (93%) with complete ENL control during the initial year maintained complete control at year 3.

Many patients who demonstrated only partial ENL control during year 1 of thalidomide treatment achieved complete control at years 2, 3 and 5 (59%, 67% and 80%, respectively).

A higher complete control rate was achieved in patients on lower doses of thalidomide: complete control was seen in 83% of 900 patients on ≤100 mg/day, 68% of 377 patients on 101–200 mg/day, and 68% of 59 patients on 201–300 mg/day.

Prevention of relapse

A subset of patients (n=102) from the US monitoring programme with ENL controlled by thalidomide have demonstrated repeated cycles of relapse after drug withdrawal and remission with reinstitution of therapy.

These results show that thalidomide treatment is useful for preventing the relapse of ENL symptoms. A general finding from this programme is that, following initial thalidomide treatment, a maintenance dose of 25–200 mg/day was effective in preventing recurrent reactions.

The findings of this long-term retrospective analysis, together with the results of the controlled trials described above, demonstrate the efficacy of thalidomide in the treatment of ENL and its clinical manifestations.

Multiple Myeloma and the Role of Thalidomide

Multiple Myeloma

Epidemiology

Multiple myeloma is defined as a malignancy of terminally differentiated B-lymphocytes. The condition is characterised by the clonal proliferation of plasma cells that are innately resistant to standard-dose chemotherapy, and although alternative treatments are available, multiple myeloma is rarely cured.[31]

Multiple myeloma accounts for 1% of all cancers, 10% of Caucasian haematological malignancies and 20% of Afro-Caribbean haematological malignancies.[31] The median age at diagnosis is 71 years, and US data estimate that the overall annual incidence is 4 cases per 100,000 population.[31] In addition to the racial discrepancies, multiple myeloma is associated with a male to female ratio of 1.4:1; it is not fully known why these ethnic and gender differences exist.[31] The number of multiple myeloma cases is rising, due in part to the aging population. In the USA, in 2001, there were approximately 14,400 new cases diagnosed and 11,200 deaths.[32] The rate is similar in the European Union, with about 16,000 new cases per year.

Pathophysiology

The aetiology of multiple myeloma is unknown, but a number of risk factors have been identified. These include: chronic immune stimulation, autoimmune disorders, exposure to ionising radiation, and occupational exposure to pesticides, herbicides, or dioxin.[31] There is also a strong viral aetiological link, with HIV patients having a 4.5-fold increased likelihood of developing the condition.[33]

Multiple myeloma is characterised by a diffuse population of malignant plasma cells scattered through the bone marrow. These cells produce an abnormal monoclonal protein, also known as the M protein or paraprotein. A pathophysiological model for multiple

myeloma was proposed by Hallek et al. in 1998.[34] This comprises an ordered progression from a normal plasma cell to monoclonal gammopathy of undetermined significance (MGUS) to multiple myeloma. Osteoclastic activity is increased, possibly as a result of the action of locally produced osteoclastic stimulating factors such as IL-1 and IL-6. IL-6 is essential for the survival and growth of myeloma cells, which express specific receptors for this cytokine. It is thought that IL-6 not only acts as a myeloma cell growth factor, but also promotes myeloma cell survival by preventing spontaneous or dexamethasone-induced apoptosis. IL-6 receptors are present in high concentrations in the serum of patients with myeloma, especially in those with a poor prognosis.[31]

Clinical manifestations

In 75% of patients, multiple myeloma is associated with bone pain, and osteolytic lesions and compression fractures are often seen in the axial skeleton and proximal long bones. The increased bone resorption associated with multiple myeloma often leads to hypercalcaemia, which may manifest as lethargy, nausea and constipation. 'Myeloma kidney' can also develop – a condition in which the distal convoluted tubules and collecting ducts become obstructed, culminating in renal insufficiency.

Cytokine dysregulation leads to erythropoiesis, which results in anaemia in approximately 75% of patients. However, this is usually treatable, with ~60% of patients responding to exogenous erythropoietin.[31]

In multiple myeloma, overall survival primarily depends on the biology and stage of disease, and the status of the patient's kidneys. Typically, patients in the early stages of disease have a better prognosis than those in later stages. Similarly, patients with fully functioning kidneys can expect longer survival than those with severe renal dysfunction. In 1975, the Durie–Salmon Staging System was

published to distinguish patients with low (Stage I), intermediate (Stage II) and high (Stage III) volumes of tumour mass before initiation of therapy. These stages are further divided into sub-stages A (serum creatinine <2 mg/dl, <180 μmol/L) and B (serum creatinine ≥2 mg/dl, ≥180 μmol/L). In addition, recent advances in our understanding of the biology and treatment of myeloma have led to the use of the following clinically significant prognostic parameters:[31]

Favourable prognostic factors in multiple myeloma

β-2 microglobulin ≤2.5 mg/L
C-reactive protein ≤4.0 mg/dl
No -13/13q- chromosome abnormalities
Plasma cell labelling index <1%
Absence of plasmablastic morphology
≤12 months' prior treatment
Chemotherapy-sensitive disease
Any complete remission
Non-IgA isotype
Low IL-6 receptor density

The strongest predictors of a favourable outcome (that are routinely available) are low β-2 microglobulin and C-reactive protein.[31]

Treatment Options

The treatment of multiple myeloma is categorised according to the type of therapy administered. To help decide upon the most appropriate course of action, patients are normally carefully evaluated in terms of symptoms, physical findings and laboratory data. If there are no symptoms or evidence of early or impending complications, the patient should not be treated. Treatment should instead be delayed until disease progression is observed.[35]

The two principal types of therapy are cytoreductive therapy and supportive care.

Cytoreductive therapy

Cytoreductive therapy is designed to reduce the number of myeloma cells and includes the following:

Melphalan and prednisone (M/P)

Melphalan and prednisone have been the gold standard for treatment over the last 30 years.[36] The introduction of this chemotherapy regimen increased median survival from 7 months to 24–30 months.[31] Melphalan and prednisone combinations usually achieve response rates of around 50–60% in patients with multiple myeloma,[37] but only 5% of patients achieve complete remission.[31] Typical doses are melphalan 0.15 mg/kg/day and prednisone 20 mg three times daily for 7 days. The regimen is usually repeated every 6 weeks.

Vincristine, doxorubicin and dexamethasone (VAD)

This is the standard induction regimen for patients who are suitable for stem cell transplantation. It is also used when patients are initially refractory to M/P. Response rates of between 60–70% have been observed in patients who become resistant to alkylating agents, but to date no long-term survival benefit has been seen over M/P.[37] It is also unclear whether VAD is more efficacious than dexamethasone monotherapy.

Peripheral blood stem cell transplantation

Peripheral blood stem cell transplantation (PBSCT) is known to improve overall survival in multiple myeloma. Stem cells are harvested from the peripheral blood via a process called apheresis. High-dose chemotherapy is administered to the patient, with the intention of ablating the malignant plasma cells in the bone marrow microenvironment. The patient's stem cells are then re-injected to help boost the immune system.

In 1996, French investigators compared this approach to conventional chemotherapy and conclusively showed that it yielded a superior disease-free and overall survival outcome. The 5-year projected survival for the transplant group was 52% *versus* 12% for the conventional therapy cohort. Further, while complete responses were observed in only 5% of patients on conventional therapy, 22% of the transplant cohort achieved complete remission.[38]

There is some debate as to which patients are most suitable for transplantation, and the question remains regarding whether tandem or single transplantation is more beneficial.

Thalidomide

Thalidomide has recently been found to have immunomodulatory efficacy in patients with advanced multiple myeloma. Indeed, some experts believe that the use of thalidomide is the most significant advance in the treatment of myeloma since the introduction of high-dose melphalan and autologous stem cell transplantation nearly 20 years ago.[39] Data supporting the use of thalidomide is covered in detail in the next section of this monograph.

Supportive therapy

Supportive therapy focuses on alleviating myeloma-associated symptoms such as bone damage. Bisphosphonates are the mainstay of supportive care. Following administration, bisphosphonates bind tightly to exposed bone mineral around resorbing osteoclasts, leading to very high local concentrations (up to 1 mM) of bisphosphonates in the resorption lacunae. On release from the bone surface, bisphosphonates are taken up by the osteoclast, where they cause disruption of the biochemical process involved in bone resorption and osteoclast apoptosis.

Two bisphosphonates have shown promise in the treatment of multiple myeloma. Pamidronate is an intravenous agent which is administered monthly, while zoledronic acid is a newer, more potent bisphosphonate with a shorter infusion time.

In a long-term study by Berenson et al.,[40] 392 myeloma patients were randomised to receive monthly 4-hour infusions of either placebo or pamidronate (90 mg) for 21 cycles. Initial results after 9 cycles showed that, compared with placebo, the proportion of patients who reported a skeletal event was significantly lower in the pamidronate group. Unlike placebo, patients receiving pamidronate also showed decreases in bone pain, no increase in analgesic usage and no deterioration in performance status or quality of life. The results after an additional 12 cycles showed that, compared with placebo, the pamidronate cohort contained significantly more skeletal-event-free patients, although no differences in overall survival were observed.

Zoledronic acid is the most potent bisphosphonate developed to date, being approximately 100 to 1,000 times more active than pamidronate. In a recent study, 1,648 patients with multiple myeloma or breast cancer, and with at least one osteolytic bone lesion, were randomised to receive either a 2-hour infusion of 90 mg pamidronate disodium or a 15-minute infusion of either 4 or 8 mg zoledronic acid. Infusions were administered every 3 to 4 weeks for 12 months.[41] Zoledronic acid was found to control bone metastases with equal efficacy to pamidronate. Time to first adverse skeletal event (i.e. spinal cord compression, fracture, need for surgery and/or occurrence of hypercalcaemia) was also compared. Patients in the zoledronic acid group did not suffer their first event until day 372, whereas in the pamidronate group an initial adverse event was seen, on average, after 301 days. Both agents were well tolerated.[41]

Clinical Efficacy of Thalidomide in Multiple Myeloma

Thalidomide monotherapy

The use of thalidomide as an anti-myeloma agent was first investigated in 1999 by Singhal et al.[42] A starting dose of 200 mg/day was administered to 84 previously treated patients with refractory myeloma. This dose was then increased in fortnightly increments of 200 mg, up to a maximum of 800 mg/day. The median study duration was 80 days. All patients had responded poorly to conventional chemotherapy and most were in relapse and/or had been pre-treated with at least one course of high-dose chemotherapy or stem cell rescue. Primary efficacy measures were median overall survival and a reduction in serum myeloma protein of at least 25%. Thalidomide evoked a response rate of 32% and a median overall survival of 14 months. Responses were associated with a reduction in bone marrow infiltration by plasma cells and improved haemoglobin levels, indicating a true anti-tumour effect. For the 42% of patients lacking chromosome 13 abnormalities (a high-risk cytogenetic factor), the response rate was higher (44%), with a 2-year survival rate of 47%. Data suggest that with non-thalidomide salvage regimens, the expected median overall survival for this patient cohort is normally less than 14 months. The authors concluded that thalidomide had substantial anti-tumour activity in patients with advanced myeloma.

A recently published study by Barlogie et al.[43,44] reinforced these findings and indicated that thalidomide monotherapy produces a durable therapeutic response. In an extension to the previous trial, the investigators analysed 169 patients with advanced myeloma, all of whom followed the dosing regimen outlined above. A 25% reduction in myeloma protein was observed in 37% of patients, a 50% reduction in 30% of patients, and near-complete or complete remission in 14%. Two-year event-free and overall survival rates were 20 ± 6% and 48 ± 6%, respectively. Thromboembolic events occurred

in fewer than 5% of patients. Moreover, the investigators noted that response rates were higher and survival times longer in patients who received more than 42 g thalidomide over the 3-month study period. This was especially apparent in high-risk patients, prompting the authors to conclude that a thalidomide dose–response relationship exists in advanced myeloma.

These initial results have since been followed up with 4-year data. Fifty per cent of patients achieved a myeloma protein reduction of at least 25%, while 33% achieved a response of a least 50%. Furthermore, 11% of patients achieved either a complete response or near-complete response. At 4 years, 9% of patients remained event-free and 25% were still alive.

Importantly, other investigators have repeated these findings. Overall, results have shown that between 25% and 53% of patients with relapsed or refractory disease achieve a partial response, confirming the efficacy of thalidomide as monotherapy in advanced multiple myeloma.[45-53]

A retrospective analysis by Wechalekar et al.[52] concluded that intermediate-dose thalidomide also had significant efficacy in relapsed myeloma. Thirty-seven patients with relapsed myeloma were included in the analysis. All patients received thalidomide 200 mg/day, and no subsequent dose escalation was performed. The response rate was found to be 44%. The most commonly reported adverse events were fatigue (54%), sleepiness (48%), constipation (43%), neuropathy (24%) and dizziness (10%). Thirteen per cent of patients withdrew from the study. The authors concluded that at this dosage, tolerability appeared to be superior to that of standard-dose therapy.

Thalidomide has also been investigated in untreated, asymptomatic patients. A study by Rajkumar et al.[47] reported a response rate of 38% and a median overall survival of over 12 months.

All principal studies involving thalidomide monotherapy in myeloma patients are summarised in Table 3.

Table 3. Response rates with thalidomide monotherapy in relapsed or refractory multiple myeloma patients (adapted with permission; Cavenagh & Oakervee[39])

Number of patients	Response rate (>25% reduction in M protein)	Reference
84	32%	Singhal et al.[42]
169	37%	Barlogie et al.[43,44]
23	52%	Juliusson et al.[45]
32	31%**	Rajkumar et al.[46]
32	53%	Oakervee et al.[48]
120	32%	Grosbois et al.[49]
44	25%	Weber et al.[50]
36	44%	Durie & Stepan[51]
37	44%	Wechalekar et al.[52]
169	50%	Barlogie et al.[53]
16*	38%**	Rajkumar et al.[47]

*Untreated, asymptomatic patients; **>50% reduction in M protein only reported.

Thalidomide plus dexamethasone

The activity of thalidomide as a single agent has encouraged investigations of thalidomide and dexamethasone combination therapy in patients with advanced myeloma.

A study by the MD Anderson Cancer Center administered this combination in 26 non-responders to thalidomide monotherapy. Thirty-five per cent of patients responded to the treatment, indicating that the two agents evoked a clinical synergy.[50] Two smaller studies reinforced these findings, reporting response rates of 26% and 48% with the combination of thalidomide (≤600 mg/day) and pulsed dexamethasone.[54,55] In the latter study, this combination was found to evoke similar efficacy rates to dual therapy with melphalan and prednisone. The thalidomide and dexamethasone combination was also associated with lower toxicity rates.

These data have prompted studies in patients with newly diagnosed multiple myeloma. A major potential advantage of this regimen is that it obviates the need for a long-term central venous catheter, with its associated risks of infection and line-related thrombosis. An initial study of 50 patients with active myeloma reported response rates of 64%.[56] Further studies are planned.

Table 4 summarises the clinical trials published to date involving thalidomide and dexamethasone combination therapy.

Table 4. Response rates with thalidomide and dexamethasone combination therapy in relapsed or refractory multiple myeloma patients (adapted with permission; Cavenagh & Oakervee[39])

Number of patients	Response rate (>50% reduction in M protein)	Reference
26	35%	Weber et al.[50]
27	26%	Tosi et al.[54]
44	48%	Palumbo et al [55]
7	43%	Durie & Stepan[51]
50*	64%	Rajkumar et al.[56]

*Newly diagnosed patients.

Thalidomide plus chemotherapy

Data relating to the combined use of thalidomide, dexamethasone and chemotherapy also show promise. A study by Kropff et al.[57] investigatec the combination of hyperfractionated cyclophosphamide, dexamethasone and thalidomide (Hyper-CDT) in 14 patients with advanced myeloma. Twelve patients (86%) achieved a partial response and were maintained on thalidomide and dexamethasone combination therapy. No disease progression was observed after a median of 7 months, and no excess of thrombotic effects was reported.

Similarly, a study by Moehler et al.[58] investigated the effects of thalidomide, cyclophosphamide, etoposide and dexamethasone (T-CED)

in 42 patients with advanced myeloma. A partial response rate was reported in 78% of these patients.

Another approach in advanced disease has been to combine low-dose thalidomide (50–200 mg) with dexamethasone and clarithromycin (BLT-D). In an unpublished study by Coleman et al., 55 patients were treated with this regimen. Of 40 evaluable patients, 93% had at least a partial response, while 13% achieved complete responses.[39]

The largest study to investigate patient survival involved 236 previously treated patients, and was undertaken by US researchers. The group of patients taking chemotherapy was initially treated with two cycles of dexamethasone, thalidomide, infusional cisplatin, doxorubicin, cyclophosphamide and etoposide (DT-PACE). Partial responders were then randomised to receive further DT-PACE cycles or tandem autograft procedures. The 2-year event-free survival rates in these two groups were 63% and 65%, respectively, with overall survival rates of 81% and 79%. The number of thromboembolic events was not unexpectedly high. It is difficult to draw firm conclusions from this study as 58% of patients in the further DT-PACE arm crossed over to the tandem autograft arm because of failure to achieve pre-defined levels of response.

The researchers concluded that DT-PACE was an excellent induction regimen for previously treated myeloma patients, but that high-dose therapy is still required for durable disease control.[59]

Further data from other studies are summarised in Table 5.

Table 5. Response rates with combined thalidomide therapy and chemotherapy (adapted with permission; Cavenagh & Oakervee[39])

Regimen	Number of patients	Response rate (>50% reduction in M protein)	Disease type
Hyperfractionated cyclophosphamide, dexamethasone, thalidomide[57]	14	86%	Advanced
Thalidomide, cyclophosphamide, etoposide, dexamethasone[58]	42	78%	Advanced
Pulsed thalidomide, cyclophosphamide, dexamethasone[60]	24	50%	Previously treated
Thalidomide, vincristine, adriamycin, dexamethasone[61]	12	100%	Newly diagnosed*
Melphalan, prednisone, dexamethasone[62]	13	38%	Newly diagnosed
Melphalan, prednisone, dexamethasone[62]	9	44%	Advanced
Clarithromycin, low-dose thalidomide, dexamethasone (Coleman et al. 2001 [unpublished])	55	93%	Advanced

*One patient had advanced disease.

Safety and Tolerability of Thalidomide

Clinical Experience in the Use of Thalidomide

Thalidomide was introduced in Europe during the 1950s as a sedative agent and was found to be particularly effective at alleviating the symptoms of morning sickness. As is widely known, thalidomide was subsequently withdrawn in 1961 after its teratogenic properties were recognised. Since that time, thalidomide's immunomodulatory and anti-angiogenic effects have been established and it has been used in a restricted manner in the treatment of patients with erythema nodosum leprosum (ENL) and HIV-related conditions. Thalidomide has also been administered investigationally for more than 20 years in a variety of solid and haematological malignancies, and has been shown to be particularly effective in the treatment of advanced multiple myeloma.

Overview of Adverse Events

The adverse event profile of thalidomide has been determined from controlled clinical trials in ENL and HIV-related conditions, from uncontrolled investigational experience with thalidomide in patients with ENL and in patients who are HIV-seropositive, and from additional events identified in the published literature or from anecdotal reports from other sources involving the investigational use of thalidomide in other indications.[2]

The most serious toxicity associated with thalidomide is its documented teratogenicity, which can occur if even one dose of thalidomide is taken during pregnancy.[4] Peripheral neuropathy is a common, potentially severe side effect that may be irreversible.[63] Hypersensitivity reactions have also been reported. Caution should be used when thalidomide is combined with chemotherapy, as venous thromboembolism is a potential complication.[56] Several laboratory abnormalities are associated with the use of thalidomide, including neutropenia and increases in viral load. The most commonly observed adverse reactions associated with thalidomide are constipation,

somnolence and asthenia. The adverse events for which a causal relationship with thalidomide could reasonably be established are listed in Table 6. Frequencies given are based mainly on the observations during investigational studies and on experience with the drug in the USA.

Table 6. Adverse events for which a causal relationship with thalidomide could reasonably be established (data on file)

	Very common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1,000, <1/100)	Rare (>1/10,000, <1/1,000)	Very rare (<1/10,000)
Blood and lymphatic system disorders		Neutropenia Leukopenia			Eosinophilia Thrombocytopenia Anaemia
Metabolism disorders				Increased appetite	
Psychiatric disorders		Mood changes			Decreased libido Confusion
Nervous system disorders	Somnolence Peripheral sensory neuropathy	Dizziness Paresthesia Drowsiness Headache	Tremor		Seizures
Cardiac disorder				Cardiac arrhythmia Bradycardia Tachycardia	
Vascular disorders				Deep vein thrombosis*	Thromboembolic events Orthostatic hypotension
Gastrointestinal disorders		Constipation Dry mouth Nausea			Intestinal obstruction
Skin disorders		Rash Urticaria			Pruritis Dry skin Bullous skin reactions Stevens–Johnson syndrome Toxic epidermal necrosis Facial oedema Photosensitivity
Endocrine disorders					Hypothyroidism
Respiratory, thoracic and mediastinal disorders			Dyspnoea		Bronchospasm
Reproductive system disorders					Menstruation disorders
Foetal development disorders		Teratogenicity			
General disorders		Asthenia Peripheral oedema Weakness Fatigue Lethargy		Malaise	

*Deep vein thrombosis may occur more frequently in malignant conditions (see page 38)

Teratogenicity

If thalidomide is taken during pregnancy it can cause severe birth defects or death to the unborn baby. The risk of teratogenicity is extremely high during a critical period of pregnancy, estimated to be 34 to 50 days after the beginning of the last menstrual period.[3] The risk of birth defects outside this critical period is unknown, but may be significant.

Although there is no one particular birth defect caused by thalidomide therapy, the nature and pattern of defects are, in most cases, similar enough to be recognisable as thalidomide-induced.[3] The range of abnormalities include amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia and microtia), facial palsy, eye abnormalities (anophthalmos and microphthalmos) and congenital heart defects. Gastrointestinal and renal anomalies have also been documented.[64] Mortality at or shortly after birth is approximately 40%; death is often the consequence of serious internal organ defects.[3]

Peripheral neuropathy

Peripheral neuropathy is a common, potentially severe side effect of thalidomide treatment. Neuropathy is characterised by distal axonal degeneration. Sensory symptoms are symmetrical and usually affect the distal lower limbs. Symptoms may include painful paresthesias of the hands and feet, hyperesthesia or a sensation of 'tightness' around the feet. If therapy continues, paresthesias of the feet will gradually become permanent and progress up the legs; the same symptoms may occur in the hands and progress proximally. Patients may experience muscle cramps, muscle weakness, postural tremor, decreased muscle stretch reflex, pallor and coldness.[63,65]

Symptoms may improve when thalidomide is discontinued; however, neuropathy can be irreversible if the drug is not promptly withdrawn.[39] In a study evaluating the electrophysiological effects associated with thalidomide-induced peripheral neuropathy in 13 patients with discoid lupus erythematosus, the most prominent electrophysiological alteration was decreased sensory nerve action potential amplitude in the sural nerve; improvement in clinical symptoms was not necessarily associated with resolution of electrophysiological abnormalities.[65]

Some studies have indicated an increased risk of neuropathy with advanced age and a cumulative thalidomide dose >40–50 g.[63,66] However, peripheral neuropathy can occur at a lower cumulative dose, suggesting that the patients' underlying condition or predisposition may play a part.[67,68]

It is recommended that clinical and electrophysiological examinations be performed in patients prior to, or within one month of, starting thalidomide therapy, and that routine monitoring is carried out after 6, 12 and 18 months and annually thereafter during treatment. Patients should be advised to report prickling, numbness or paraesthesia. Patients should be questioned monthly and clinically evaluated for signs or symptoms of peripheral neuropathy, such as numbness, tingling or pain in the hands and feet. Should symptoms of peripheral neuropathy be observed, consideration should be given to electrophysiological testing, consisting of the measurement of sensory nerve action potential (SNAP) amplitudes.

If drug-induced neuropathy is confirmed, discontinuation of thalidomide is necessary to limit further damage. Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide (e.g. zalcitabine, didanosine and stavudine).

Venous thromboembolism

In malignant conditions, such as multiple myeloma, patients are predisposed to a hypercoagulable state and venous thromboembolism has emerged in association with thalidomide therapy in this setting.

The frequency of venous thromboembolism with thalidomide monotherapy in patients with multiple myeloma has generally been less than 5%.[39] The risk appears to be increased when thalidomide is used in combination with chemotherapy; a retrospective analysis of thalidomide-treated multiple myeloma patients reported rates of thromboembolic events of 30.9% among 110 patients who received thalidomide plus chemotherapy *versus* only 4.6% among 326 patients who received thalidomide alone.[69] An unexpectedly high risk of venous thromboembolism has been observed when thalidomide is combined with chemotherapy for newly diagnosed patients with myeloma. Rajkumar et al.[56] reported a 10% incidence of venous thromboembolism when thalidomide was combined with dexamethasone as initial therapy in 50 patients with newly diagnosed myeloma;[56] this was higher than that observed when the same regimen was used in relapsed or refractory patients. A summary of clinical trials reporting venous thromboembolic events in multiple myeloma patients on thalidomide-based therapy is provided in Table 7.

Some authors have recommended prophylactic anticoagulation if thalidomide is to be given in combination with chemotherapy.[71] Additionally, all patients with increased plasma viscosity should be considered for appropriate prophylaxis; although preliminary observations suggested that prophylactic low-dose warfarin may be effective,[44] it is now recognised that patients require low molecular weight heparin (LMWH) to reduce the rate of venous thromboembolism in patients receiving thalidomide simultaneously

Table 7. Incidence of venous thromboembolism in multiple myeloma patients treated with various thalidomide-based treatment regimens (adapted with permission; Cavenagh & Oakervee [39])

Regimen	Incidence of venous thromboembolism (%)	Newly diagnosed or advanced disease
Thalidomide monotherapy[43]	<5%	Advanced
Thalidomide monotherapy[69]	5%	Not reported
Thalidomide, dexamethasone[56]	10%	Newly diagnosed
Thalidomide, dexamethasone[69]	15%	Not reported
Thalidomide, chemotherapy[69]	31%	Not reported
Thalidomide, vincristine, adriamycin, dexamethasone[61]	33%	Newly diagnosed
Thalidomide, melphalan, prednisolone[62]	23%	Newly diagnosed
Thalidomide, melphalan, prednisolone[62]	11%	Advanced
Thalidomide, adriamycin, dexamethasone[70]	26%	Newly diagnosed
Thalidomide, chemotherapy[71]	28%	Newly diagnosed

with chemotherapy.[71] Furthermore, such combination treatment has been safely continued in patients with venous thromboembolism once therapeutic anticoagulation (LMWH followed by warfarin with target INR of 2.5–3) has been established.[71]

Sedation

Thalidomide was initially developed as a sedative; accordingly, the most common adverse event associated with its use is somnolence. Thalidomide causes dose-related somnolence by activating diencephalic sleep centres without depressing CNS neuronal function.[72] The incidence of somnolence reported from clinical trials in patients with ENL treated with thalidomide 50–300 mg/day was 37.5%.[2] Sedative effects may manifest as a morning drug 'hangover', dizziness, fatigue, mood changes and weakness. To minimise these effects, the drug is usually administered in the late evening or at bedtime; decreasing the dose may also reduce morning drowsiness. Tachyphylaxis to the sedative effects of thalidomide has been noted after the second or third week of therapy;[73] however, in many cases, somnolence may be dose-limiting or result in discontinuation of therapy.[74]

Hypersensitivity

Hypersensitivity reactions to thalidomide have been reported.[75,76] The occurrence of mild to severe thalidomide-induced rash may be dependent on the patients' immune status and underlying disease state. The most common rash described in association with thalidomide use is typically pruritic, erythematous and macular and occurs on the trunk, back and proximal extremities;[1] it is most likely to occur after 10–14 days of thalidomide therapy and does not appear to be dose-related.[74]

In a review of studies involving patients with ENL who received thalidomide 50–300 mg/day, the incidence of rash was 25%.[2] In a study of patients with multiple myeloma, rash occurred in 16–26% of patients receiving thalidomide doses of 200–800 mg/day.[42] A less frequently occurring and more severe rash is accompanied by systemic signs and symptoms (e.g. fever, chills, tachycardia, hypotension and eosinophilia); in very rare cases this may develop into Stevens–Johnson syndrome or toxic epidermal necrolysis.

Discontinuing therapy as soon as rash is recognised usually brings prompt relief. Symptomatic relief of pruritus may be achieved with antihistamines or topical corticosteroids, although this has not been evaluated in controlled trials. Continuation of therapy can result in a more severe reaction.[77] In some treatment populations, drug re-challenge has been reported to bring about a more severe and immediate reaction; in one study, a severe sepsis-like reaction occurred in HIV-infected patients after re-challenge with thalidomide.[74] Re-challenge should not be attempted if the rash is exfoliative, purpuric or bullous, or if Stevens–Johnson syndrome or toxic epidermal necrolysis are suspected.

Constipation

Constipation is a common complication of thalidomide therapy, with a reported incidence ranging from 3 to 30% of patients;[78]

the incidence may be greater at higher dosages.[42] Although the mechanism by which thalidomide causes constipation is unknown, it is suspected to involve neuromuscular colonic inertia with hypotonia.[72] In addition to routine measures such as increased fluid intake and a high-fibre diet, management of thalidomide-induced constipation has generally involved the use of mild laxatives or temporary discontinuation of therapy.[79] Some investigators have also used laxatives prophylactically.[73]

Laboratory Abnormalities

Neutropenia

Decreases in white blood cell counts below pre-treatment levels have been reported in association with the clinical use of thalidomide. In a study of 80 patients receiving thalidomide for graft-*versus*-host disease, neutropenia occurred in 18% of patients.[75] Neutropenia resolved after drug therapy was discontinued, but recurred in 6 patients on re-challenge. In another study of 84 patients receiving thalidomide for multiple myeloma, <5% were reported to have leukopenia.[42]

The baseline white blood cell count should be determined before initiation of thalidomide, and treatment should be withheld in patients with an absolute neutrophil count (ANC) of <750/mm^3 (0.75 x 10^9/L). If the count falls below 500/mm^3 during thalidomide treatment, the drug should be discontinued. In patients prone to neutropenia, e.g. HIV and myeloma patients, white blood cell counts should be monitored on an ongoing basis.

Increased HIV viral load

In a double-blind, placebo-controlled study, 57 HIV-seropositive patients received a 4-week course of thalidomide 200 mg/day or placebo as therapy for oral aphthous ulcers.[80] The patients in the thalidomide group had a significantly greater increase in HIV RNA

from baseline to week 4 than those in the placebo group (median increase 0.42 log_{10} *vs* 0.05 log_{10} copies/ml; p=0.04). The clinical significance of this increase is unknown.

Abuse and Dependence Potential

Physical and psychological dependence have not been reported in patients taking thalidomide.

Overdosage

There have been three reported cases of thalidomide overdosage. There have been no reported fatalities following ingestion of thalidomide doses of up to 14.4 g and all patients recovered without reported sequelae.

For information on contraindications, precautions and drug interactions associated with the use of thalidomide please refer to the Prescribing Information on page 51.

Dosage and Administration of Thalidomide

Recommendations in the Treatment of ENL

Erythema Nodosum Leprosum (adult dosage):

Dosing should be initiated at 100mg daily orally and, only where symptoms remain uncontrolled, increased by 100mg at weekly intervals according to tolerance and toxicity (see Clinical Trials section in Australian Product Information for results of Study E-003P). The maximum recommended dose is 400mg daily. Depending on tolerance and observed toxicity, lower maintenance doses can be used than those used to control the active reaction.

In patients with moderate to severe neuritis (due to leprosy) or other serious complications (e.g. uveitis), corticosteroids and other appropriate therapy may be started concomitantly and tapered/discontinued when neuritis etc has improved.

There have been no well-controlled studies of thalidomide as maintenance therapy to prevent ENL relapse to provide maintenance dosing recommendations. In study E-003P only 1 of 23 patients was tapered from treatment successfully using a 3-7 week tapering regimen. Given the risks associated with ongoing thalidomide treatment, it is suggested that tapering (with the aim of discontinuation) be attempted every 3-6 months, in decrements of 50mg every 2 to 4 weeks.

To reduce central nervous system effects (e.g. drowsiness, somnolence, sedation) during the day, this dose is normally taken as a single dose in the evening. Thalidomide Pharmion 50mg Hard Capsules should be taken at least one hour after food.

Recommendations in the Treatment of Multiple myeloma

Multiple myeloma (adult dosage):

Dosing should be initiated at 200mg daily orally and increased by 100mg at weekly intervals to a maximum dose of 800mg daily according to tolerance and toxicity. Depending on tolerance and observed toxicity, lower maintenance doses can be used

No systematic dose escalation studies have been performed in multiple myeloma patients; dosages used have varied widely between 50 mg/day and 1,200 mg/day and responses have been seen at all dosage levels.[81] The majority of patients will respond at doses of 300–400 mg or less.[39]

Singhal & Mehta[81] recommended that thalidomide should be started at a dosage of 100–200 mg/day and increased in 50–100 mg steps every week to a target dosage of 400–800 mg/day. The optimum dosage for a given patient is the one that is best tolerated by that individual

Pharmion Risk Management Programme (PRMP)

Introduction

The Pharmion Risk Management Programme (PRMP) has been developed from the Celgene System for Thalidomide Education Prescribing and Safety (S.T.E.P.S.®), which is used in the USA for controlling the distribution of thalidomide. It is a multi-component system designed to prevent any possibility of foetal exposure to thalidomide. The system also helps to raise awareness of other potential side effects that can occur during therapy with thalidomide. In the USA, the Celgene programme has been successfully used for monitoring approximately 30,000 patients over the last 4 years.

Under the Pharmion Risk Management Programme (PRMP), only physicians and pharmacies registered with the programme are allowed to prescribe and dispense thalidomide. In addition, patients must agree to register and comply with the requirements of the risk management programme in order to receive the product. Thalidomide may be prescribed by any licensed physician who is registered in the Pharmion Risk Management Programme (PRMP) and understands the risk of teratogenicity if thalidomide is used during pregnancy.

The use of thalidomide is restricted to those patients who have given their individual written agreement to use the drug as specified, by signing an informed consent form. Signature will only be obtained after the patient has been fully informed of the potential side effects and risks with the drug, including the risk of foetal death and severe birth defects and the precautions that need to be taken before, during and after thalidomide therapy.

Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment, and not to share thalidomide.

Before prescribing thalidomide, the physician must perform all necessary investigations and inquiries (as outlined in the Pharmion

Risk Management Programme [PRMP]) and determine that the potential benefits to the patient outweigh the potential risks of its use.

Programme Overview

A physician who wants to start using thalidomide in a given patient must first register with the Pharmion Risk Management Programme (PRMP) as a primary prescribing physician. After having carried out all necessary patient eligibility checks and having obtained the patient's informed consent, the primary prescribing physician also registers the patient with the Pharmion Risk Management Programme (PRMP).

After registering the patient by faxing a copy of the consent form to the Pharmion Risk Management Centre, the prescribing physician asks female patients to phone the management centre in order to complete a patient survey – this is usually done in the physician's office. The physician also needs to take part in a telephone survey to ensure all obligations have been met with respect to testing and monitoring of the patient, and receives an authorisation number, which is then written on the prescription.

The patient takes the prescription to the pharmacy. If not already registered, the pharmacy registers with the programme. The pharmacist must phone the Pharmion Risk Management Centre to obtain authority to dispense the drug on each separate occasion. The drug is then dispensed to the patient in monthly allocations of 28 days' supply.

Monitoring Procedures

Any suspected adverse event that is observed in the patient during treatment with thalidomide or within 8 weeks after stopping the treatment must be immediately reported to Pharmion and, according to the governing regulations, to the local health authorities.

Monitoring procedures applicable in female patients

Adult females and children over 12 years not of child bearing potential

In adult female patients who report having undergone hysterectomy or who report being post-menopausal for more than 24 months, the physician must take sufficient measures to confirm hysterectomy or post-menopausal status before initiating thalidomide. In children, the physician must determine child bearing potential. In both adults and children, the physician must exclude existing pregnancy before initiating thalidomide.

Adult females and children over 12 years of child bearing potential

In the case of a female patient who has not undergone hysterectomy or who has not been post-menopausal for more than 24 months, the physician must take sufficient measures to exclude existing pregnancy before initiating thalidomide. The physician must obtain a negative result in a blood pregnancy test performed within 24 hours prior to initiating the first and each monthly prescription. Patients must be adequately counselled regarding the use of contraception every time a prescription is issued.

Any female patient who is of child bearing potential must use reliable contraceptive methods for at least one month before starting thalidomide treatment, during treatment, and for one month following termination of treatment. Reliable contraception in female patients means the use (at the same time) of at least one highly effective method of contraception (intra-uterine device, hormonal contraception, tubal ligation or partner's vasectomy) and at least one additional effective method (diaphragm, cervical cap or condom by her male partner). If the physician considers the highly effective methods to be contraindicated, the patient may use two effective methods of contraception at the same time.

Monitoring procedures applicable in all male patients

Male patients must be instructed to use a condom with every heterosexual intercourse, even if they have undergone a successful vasectomy, as thalidomide is present in semen. Patients must be counselled on the risks of birth defects, other adverse events and important precautions required to minimise the risk related to thalidomide therapy. Male patients should use a condom with every sexual intercourse with a partner of child bearing potential.

Repeat Prescriptions

Patients returning to the physician's office for subsequent prescriptions should: receive counselling about appropriate contraception and the adverse events associated with thalidomide therapy; have a pregnancy test (if the patient is a woman of child bearing potential); and complete a telephone survey where scheduled. Once the patient (if necessary) and physician have both completed the surveys, the physician can prescribe a further 28 days' treatment.

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Product Information

THALIDOMIDE PHARMION 50MG HARD CAPSULES

Teratogenic effects:

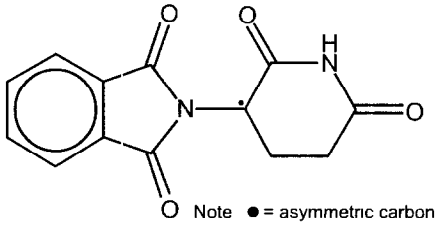
Thalidomide has caused severe birth defects when taken during pregnancy. Thalidomide should never be used by women who are pregnant or who could become pregnant whilst taking the drug or could become pregnant within 4 weeks after stopping the drug. Even a single dose can cause birth defects.

NAME OF THE DRUG:

Thalidomide Pharmion 50mg Hard Capsules

DESCRIPTION:-

Each capsule contains 50mg of thalidomide Thalidomide is 2-(2,6-dioxo-3-piperidinyl)-1H-iso-indole-1,3(2H)-dione The structural formula is



Note ● = asymmetric carbon atom

CAS No: 50-35-1

Molecular formula $C_{13}H_{10}N_2O_4$

Relative molecular mass 258 23

Thalidomide is a white to off-white powder Thalidomide is practically insoluble in water, more soluble in ethanol and acetonitrile and very soluble in DMF and DMSO It has a partition coefficient in octanol/water at room temperature of about 5

Thalidomide contains one single asymmetric carbon atom, alpha to the phthalimido nitrogen The molecule can, therefore, exist in either of two complementary optically active forms Thalidomide used in the Thalidomide Pharmion 50mg Hard Capsules formulation is a racemic mixture containing an equal amount of the S(-) and R(+) forms and therefore has a net optical rotation of zero

PHARMACOLOGY:-

The mechanism of action of thalidomide has not been confirmed. Several possible mechanisms have been proposed, based on *ex vivo* and *in vitro* studies

In patients with multiple myeloma the potential modes of thalidomide's activity include direct inhibition of myeloma cell growth and survival, anti-angiogenesis, suppression of the production of tumour necrosis factor-α (TNF-α), inhibition of selected cell surface adhesion molecules that assist leukocyte migration, shifts in the ratio of CD4+ lymphocytes (helper T cells) to CD8+ lymphocytes (cytotoxic T cells), and effects on interleukins (IL) and interferon-γ

The rationale for the use of thalidomide in patients with erythema nodosum leprosum (ENL) relates to its effect on TNF-α Patients with systemic ENL demonstrate higher serum TNF-α levels which decrease significantly during thalidomide treatment Thalidomide therapy reduces TNF-α levels in ENL patients and there is good evidence from clinical trials that thalidomide reduces the cutaneous symptoms and fever seen in ENL However, the mechanism of action of thalidomide in this indication is not well understood and other multiple immune system mechanisms, of uncertain clinical significance, have been advanced to explain thalidomide's activity in ENL

Thalidomide does not consistently reduce TNF-α levels in all disease states, and, in fact, thalidomide may increase TNF-α levels in some clinical indications It should be noted that the use of thalidomide to reduce TNF-α levels in a group of patients with toxic epidermal necrolysis, resulted in an unexpected increase in TNF-α levels and considerably increased mortality compared to placebo

Pharmacokinetics

Absorption:

Single dose studies reveal that thalidomide is slowly absorbed from the gastro-intestinal tract It exhibits linear and dose proportional pharmacokinetics over a single dose range of 50mg to 400mg in terms of the extent of the absorption (AUC0-∞) only The effect of food on the extent of absorption is probably minimal but has not been reliably established

The pharmacokinetic profile following multiple dosing (for 18 days) in pre-menopausal healthy female volunteers is similar to that following a single dose (200mg) A C_{max} value of 2 3 μg/mL was achieved approximately 5 hours after single or multiple dosing, with an elimination half-life of 4 1 - 4 5 hours No evidence of accumulation or induction of metabolism was observed

Following a single dose of 400mg thalidomide to healthy volunteers, a peak plasma concentration of 2 82 ± 0 80 μg/mL was measured at 4 3 ± 1 6 hours, with an elimination half-life of 7 29 ± 2 62 hours Pharmacokinetic data in ENL patients is limited to only 6 patients, however there appears to be a higher absorption of thalidomide in ENL patients with C_{max} of 3 44 ± 1 81 μg/mL, T_{max} of 5 7 ± 1 5 hours and an elimination half-life of 6 86 ± 1 17 hours Pharmacokinetics have not been studied in myeloma patients

Distribution:

The exact distribution profile of thalidomide has not yet been characterised in humans

Thalidomide has been shown to be present in the semen of male patients (see Precautions - Contraceptive requirements)

In human blood plasma, the geometric mean plasma protein binding was 55% and 66% respectively for (+)-(R) and (-)-(S)-thalidomide The exact volume of distribution is unknown

Metabolism:

At the present time, the exact metabolic route and fate of thalidomide is not known in humans The drug is eliminated almost exclusively by spontaneous (non-enzymatic) hydrolysis in vivo with subsequent elimination of the breakdown products in the urine There is minimal hepatic metabolism and renal excretion of thalidomide

Elimination:

The mean elimination half-life of thalidomide was shown (in single dose studies using doses between 50mg and 400mg) to be between 5 and 7 hours Less than 1% of the dose was excreted unchanged in the urine and no thalidomide was detected in urine beyond 48 hours Less than 0 1% of the dose excreted was as the 4-OH-thalidomide metabolite which was not detected in urine after 12 – 24 hours Apparent total clearance (Cl/F) is approximately 10 4 L/h and apparent renal clearance was found to be 0 08 L/h The mean half-life of elimination observed in the single dose studies was not altered upon multiple dosing

There are no data on the pharmacokinetics of thalidomide in renal or hepatic impairment

Clinical trials:

Multiple Myeloma

Two studies of thalidomide in the treatment of refractory or relapsed multiple myeloma patients (UARK98-003, Mayo 98-80-13) were performed under an IND in the USA. These studies were non-comparative, open label studies in patients with advanced, refractory disease who had been heavily pre-treated and had limited therapeutic options available for future treatment All response results belong to a per-protocol analysis group (events only included while patients were on thalidomide monotherapy) These studies are supported by data from other open uncontrolled trials in the published literature

The primary efficacy variable in the studies was the serum and urine M-protein response The results from both studies were similar In UARK-98-003, 31 4% (53 of 169 patients) responded as judged by at least a 50% reduction in serum and/or urinary M-protein (Table 1) Overall the response was confirmed in 26 6% patients six weeks later As expected, the least favourable response rates were found in those who had relapsed within one year of their HDT/ASCT treatment The median time to response was 65 days, however the duration of the response was not determined

Table 1: Tumour response (Best SWOG M-protein response) and survival rates in Study UARK 98-003

Best SWOG M Protein Response	Refractory pts (n=97)	Relapsed pts: ≤ 6 mths (n=16)	Relapsed pts: > 6 mths (n=34)	Other pts (n=22)	All pts (n=169)
	n (%)	n (%)	n (%)	n (%)	n (%)
Objective response	33 (34%)	3 (18.8%)	13 (38.2%)	4 (18.2%)	53 (31.4%)
Confirmed response	29 (29.9%)	2 (12.5%)	12 (35.3%)	2 (9.1%)	45 (26.6%)
complete remission*	3 (3.1%)	0	2 (5.9%)	0	5 (3.0%)
remission*	17 (17.5%)	2 (12.5%)	7 (20.6%)	2 (9.1%)	28 (16.6%)
partial remission*	9 (9.3%)	0	3 (8.8%)	0	12 (7.1%)

Median Survival (mths)	22.2	5.7	37.2	Not reached	23
Two year Survival Rate (%)	45.7	25	52.4	66	47.2

* Confirmed responders were further categorised into

Complete remission (CR)	Disappearance of serum and/or urinary M proteins by serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP) and immunofixation studies. No evidence of increasing anaemia
Remission (R)	≥ 75% to 99% reduction of serum M-protein by SPEP and /or ≥ 90% to 99% reduction of urine M-protein excretion per day by UPEP
Partial remission (PR)	≥ 50% to 74% reduction of serum M-protein by SPEP and /or ≥ 50% to 89% reduction of urine M-protein excretion per day by UPEP

Mayo 98-80-13 was a smaller study where 10 of the 32 patients [31%] achieved an objective response with confirmation at least six weeks later in 19% The overall one year survival rate was 65% and the median survival time had not been reached at the time of data lock

The protocols permitted maximum daily doses of 800mg thalidomide There was a trend towards achieving a greater M-protein response rate and longer progression free survival times with increasing dosage There was a statistically significant relationship between dose and overall survival (p=0 004)

Erythema Nodosum Leprosum

Study E-003P was a randomised single-centre, double-blind study comprising two dose regimens of thalidomide in the treatment of acute manifestations of ENL Daily doses of 100mg and 300mg were studied 23 male patients were enrolled and 22 completed the 7 day treatment period. 8 of 12 (67%) patients in the 100mg/day and 6 of 10 (60%) patients in the 300mg/day group showed absence of inflamed lesions at day 7 12 of 12 patients in the 100mg/day group and 8 of 10 in the 300mg/day group showed complete or partial (>50% reduction in lesion count) response Systemic symptoms resolved in 10 of 12 patients in the 100mg/day group and 5 of 11 patients in the 300mg/day group 9 of 12 patients in the 100mg/day group who were tapered to zero mg over two weeks experienced worsening of ENL by week 7 One of 7 patients in the 300mg/day group who were tapered to 50mg/day by week 7, experienced worsening of ENL

Published studies

Iyer et al 1971 This study, co-ordinated by WHO, was a randomised, double-blind comparison in men with clearly demonstrable cutaneous manifestations of ENL The study compared the effects of 100mg thalidomide four times daily in the management of male patients with lepra reactions to 400mg acetylsalicylic acid (aspirin, ASA) also given four times daily Ninety-two male patients were included, the majority were aged between 15 and 55 years For the first course, 42 patients received aspirin and 50 patients thalidomide Overall, 214 lepra reactions were observed, 116 being treated with thalidomide and 98 with ASA

An average of 48% of patients treated with thalidomide and 21% of patients treated with ASA showed no further reaction at the end of 7 days Temperature reduction to <37°C was shown in the thalidomide group but not the ASA group A difference in clearance of lepra reaction lesions was shown to favour thalidomide for skin lesions

Sheskin and Convit 1969: This study assessed the therapeutic effects of 400mg thalidomide daily in patients experiencing lepra reactions This was a randomised, placebo controlled double-blind study assessing the effect of up to 400mg daily in patients experiencing lepra reactions

Fifty-two patients (37 male and 15 female) aged between 17 and 58 years participatec Forty-eight patients suffered from chronic lepra reactions, which had lasted over a year in forty patients One-hundred-and-seventy-three treatment regimes of one week each were administered, 85 being thalidomide and 88 placebo Twenty-five patients received four treatments, 13 received three, 13 received two and 8 were treated once Seven patients re-entered the study and were permitted more than four courses

78 of 85 (92%) thalidomide courses and 24 of 88 (27%) placebo courses led to overall improvement ($p<0.01$) For the specific manifestations, erythema nodosum and erythema multiforme, 94% of those who received thalidomide and 18% of those who received placebo had some improvement

Waters 1971 Results are reported of two studies of randomised, double blind, cross-over design The primary endpoint was the effect on corticosteroid requirements based on the clinical response to thalidomide 300mg daily

In the first study, patients were administered thalidomide 100mg three times daily or placebo for 4 weeks in a cross-over fashion The nine males who participated were aged between 21-56 years They were receiving a mean prednisolone dose of 28mg/day The ENL duration was between nine months to 3 years with continuous steroid treatment for twelve months In the second study patients were administered thalidomide 100mg three times daily or placebo for 6 weeks in a cross-over fashion Eight patients were recruited into the second study, seven of whom had participated in the first study

In the first 4 week assessment period, total steroid requirements fell in the order of 60% in the thalidomide treatment period compared to the previous 4 weeks This was accompanied by improvements in the clinical and temperature scores In the second phase of the study, there was a strong trend for steroid requirements to steadily fall over the 6 weeks of thalidomide treatment

INDICATIONS:-

Thalidomide Pharmion 50mg Hard Capsules are indicated for

(1) the treatment of multiple myeloma after failure of standard therapies

(2) the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) Thalidomide is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis Thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

CONTRAINDICATIONS:-

Thalidomide Pharmion 50mg Hard Capsules are contraindicated in the following patients

- patients with known hypersensitivity to thalidomide or to any of the excipients,
- patients below 12 years of age,
- pregnant women, or those who are breastfeeding,
- women of child bearing potential who are not using, not willing or not able to use adequate contraceptive measures to prevent pregnancy,
- women of child-bearing potential where there is an alternative, treatment of non-inferior efficacy available,
- males who are not able or willing to comply with adequate contraceptive measures,
- severe neutropenia - thalidomide treatment should not be initiated in patients with an absolute neutrophil count (ANC) of $<750/mm^3$ (0.75×10^9 / L)

PRECAUTIONS:-

Only specialists in the management of leprosy, with experience in the treatment of ENL, or specialists in oncology or haematology, with experience in the treatment of relapsing or refractory multiple myeloma, should initiate treatment of patients with thalidomide

Patients (or their legal guardians where appropriate) should give individual, written, fully informed consent for the use of thalidomide Fully informed consent implies good understanding of the probability and the magnitude of harms that thalidomide can cause, the need to avoid pregnancy (and an understanding of appropriate choices for contraception, where needed), the limitations of thalidomide's treatment efficacy (including the potential for treatment failure) and the existence of alternative therapies Appropriate counselling and information should be provided to the patient's sexual partner Patients should be counselled monthly regarding risks of thalidomide and precautions to be taken when using thalidomide

Teratogenicity (see Boxed Warning, Contraindications, Use in pregnancy)

Thalidomide can cause severe birth defects or death to an unborn baby if taken during pregnancy Major human foetal abnormalities related to thalidomide administration during pregnancy are amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anopthalmos, micropthalmos) and congenital heart defects Alimentary tract, urinary tract and genital malformations have also been documented Mortality at or shortly after birth has been reported at or about 40%

Patients should be instructed to take thalidomide only as prescribed and not to share thalidomide with anyone else

The following requirements concerning pregnancy testing, contraception and condom use in male patients must be followed

Pregnancy testing:

Category 1 patients:

In case of a female patient who reports having undergone hysterectomy, the physician must take sufficient measures to exclude existing pregnancy and confirm hysterectomy status, before initiating

thalidomide Whether or not these measures should include a blood pregnancy test in these patients is left to the decision of the physician depending on the patient's profile and medical history

Category 2 patients:

In case of a female patient who has not undergone hysterectomy but who reports being post-menopausal for more than 24 months, the physician must take sufficient measures to exclude existing pregnancy and confirm post-menopausal status, before initiating thalidomide Whether or not these measures should include a blood pregnancy test in these patients is left at the decision of the physician depending on the patient's profile and medical history

Category 3 patients:

In case of a female patient who has not undergone hysterectomy or who is not post-menopausal for more than 24 months the physician must take sufficient measures to exclude existing pregnancy, before initiating thalidomide as well as with every monthly prescription and at prolongation of the authorisation to receive the drug

In order for these measures to be regarded as sufficient, the physician must have obtained a negative result of a blood pregnancy test that was performed within 36 hours before delivering the first and each monthly prescription (as well as before prolongation of the authorisation to receive the drug). In female patients in whom the time of the next menstrual bleeding can reasonably be determined (i e who are having regular cycles), thalidomide should be initiated on day 2 or 3 of the menstrual cycle

It is strongly recommended that pregnancy testing be carried out weekly in the first month of treatment, then monthly in women with regular menstrual cycles or fortnightly in women with irregular menstrual cycles

Contraception requirements:

Female patients of Categories 1 and 2:

In female patients who report to have undergone hysterectomy or who have been post-menopausal for more than 24 months the physician must evaluate the risks of these patients still becoming pregnant and give advice on use of contraceptive methods

Female patients of Category 3:

A female patient who has not undergone hysterectomy or who is not post-menopausal for more than 24 months must use reliable contraceptive methods for at least one month before starting thalidomide treatment, during this treatment, and for one month following termination of this treatment Reliable contraception in these patients means that she uses **AT THE SAME TIME** at least one highly effective method of contraception (intra uterine device, hormonal contraception via oral, injection or implant routes, tubal ligation or partner's vasectomy) **AND** at least one additional effective method (diaphragm, cervical cap or latex/polyurethane condom by her male partner)

Male patients:

Thalidomide is present in semen, therefore males receiving thalidomide must always use a latex or polyurethane condom when engaging in sexual activity with women of childbearing potential (women who have not undergone hysterectomy or who have not been post-menopausal for at least 24 months) Condom use should continue for 4 weeks after cessation of thalidomide treatment In the case of a male patient with an allergy to latex or polyurethane, at least one highly efficacious method should be used by any female sexual partner Contraception should be started in this partner at least one month prior to the start of a sexual relationship with the patient, and continued throughout thalidomide treatment and for one additional month following cessation of treatment

Male patients must not donate sperm whilst taking thalidomide and for one month after cessation of treatment

Procedure for prescribing Thalidomide Pharmion 50mg Hard Capsules:

Because of the potential for severe teratogenicity, Pharmion Pty Ltd will only supply thalidomide if the prescriber, patient and dispensing pharmacist agree to participate in a programme designed to ensure that pregnant women are not exposed to the drug This programme is known as the "Pharmion Risk Management Programme" A prescriber wishing to obtain access to thalidomide for a patient must contact Pharmion Pty Ltd for further detailed information on the Pharmion Risk Management Programme

Drowsiness, somnolence and sedation:

Thalidomide frequently causes drowsiness, somnolence and sedation Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice Thalidomide may potentiate the drowsiness caused by alcohol As with any sedative medication, the potential for impaired consciousness may increase the risk for aspiration of food, vomitus and oral secretions

Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks

Peripheral neuropathy:

Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short-term use also exist The correlation with cumulative dose is unclear Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all If thalidomide is contemplated for long-term use, baseline and 6-monthly sensory nerve action potential (SNAP) data should be collected Where such monitoring is not feasible, regular clinical assessment is required,

Patients should be advised to report prickling, numbness and

paraesthesia Patients should be questioned monthly, and clinically evaluated for signs or symptoms of peripheral neuropathy such as numbness, tingling or pain in the hands and feet Should symptoms of peripheral neuropathy be observed, SNAP data should be collected

If drug-induced neuropathy is confirmed, discontinuation of thalidomide is necessary to limit further damage Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide (e g zalcitabine, vincristine and didanosine)

Thalidomide is known to cause neuritis which may be irreversible The drug potentially aggravates existing neuritis and should therefore not be used in such patients unless the clinical benefits outweigh the risks

Seizures:

Although not reported from clinical trials, seizures, including generalised clonic/tonic convulsions, have been reported during use of thalidomide in clinical practice Most of the patients had disorders that may have predisposed to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity

Dizziness and orthostatic hypotension:

Patients should be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position

Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide Treatment should not be initiated with an absolute neutrophil count (ANC) of<750/mm^3 (0 75x10^9/L) White blood cell count and differential count should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as those with myeloma or those who are HIV-seropositive If ANC decreases to below 750/mm^3 (0 75x10^9/L) while on treatment, the patient's medication regimen should be re-evaluated and consideration should be given to withholding thalidomide if clinically appropriate

Dermatological reactions:

Serious dermatological reactions including Stevens-Johnson syndrome, which may be fatal, have been reported. Thalidomide should be discontinued if a skin rash occurs Rechallenge in some treatment populations eg HIV patients, has produced a severe and immediate reaction associated with fever, tachycardia, hypotension and rash If a rash associated with thalidomide is exfoliative, purpuric or bullous or if Stevens-Johnson syndrome or Toxic Epidermal Necrolysis is suspected, the use of thalidomide should not be resumed

Impaired wound healing:

It has been suggested that thalidomide's anti-angiogenic properties may interfere with wound healing Thalidomide should not be used within 7 days of surgery where wound healing may be problematic

Thrombogenicity:

Use of thalidomide in patients with malignant neoplastic disease, including multiple myeloma, has been associated with an increased risk of deep vein thrombosis While it is known that multiple myeloma and metastatic malignant disease may augment the risk for thrombosis and thrombo-embolic events, an additional effect of thalidomide cannot be excluded in these cases Some of the other treatments for these diseases can further augment the risk for thrombo-embolic events, and the highest rates of deep vein thrombosis during treatment with thalidomide have been reported in association with doxorubicin

Consideration should therefore be given to low dose anticoagulation in patients treated for conditions known to be associated with a significant risk for thrombosis, such as high levels of paraprotein and hyperviscosity in myeloma patients, or patients who are receiving drugs with known thrombogenic potential, or in whom other risk factors for thrombosis, such as immobilisation, are present

Other warnings:

Thyroid activity should be monitored during ongoing treatment with thalidomide as cases of hypothyroidism have been reported

Patients should be instructed to take Thalidomide Pharmion 50mg Hard Capsules only as prescribed and not to share it with anyone else

Patients must not donate blood or semen whilst taking Thalidomide Pharmion 50mg Hard Capsules

Interaction with other drugs

Specific drug-drug interactions have not been studied with Thalidomide Pharmion 50mg Hard Capsules

Increase of sedative effects of other drugs:

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine Thalidomide increases the effects of morphine derivatives, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, neuroleptics, sedative H_1 antihistamines, central antihypertensives and baclofen

Medications known to cause peripheral neuropathy:

Medications known to be associated with peripheral neuropathy

should be used with caution in patients receiving thalidomide. Increased risk of peripheral neuropathy has been reported in combination with zalcitabine, vincristine and didanosine

Doxorubicin:

An increased risk for thrombosis and thrombo-embolic events has been reported in association with doxorubicin (see Precautions)

Oral contraceptives:

In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose containing 1 0mg of norethindrone acetate and 0 75mg of ethinyl estradiol were studied The results were similar with and without co-administration of thalidomide 200mg/day to steady-state levels

Important non-thalidomide drug interactions - drugs that interfere with hormonal contraceptives:

Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception Therefore, women of childbearing potential requiring treatment with one or more of these drugs must use two other effective methods of contraception

Use in children

It is not recommended to use thalidomide in patients below 12 years of age as safety and efficacy have not been established There is only limited evidence of efficacy and safety of thalidomide in children 12-17 years of age

Use in elderly

Analysis of pharmacokinetic data in healthy volunteers does not reveal any age related changes

Impaired renal or hepatic function

Specific dose recommendations in patients with renal or hepatic disease have not been established

Since renal insufficiency is common among patients with multiple myeloma as a complication of their disease, the recommended dosage in adults has been established in populations of patients including patients with reduced renal function In general, doses in patients with renal or hepatic disease should be titrated against observed tolerance and toxicity and the highest tolerated dose should be selected

Carcinogenesis, mutagenesis

Long-term carcinogenicity studies in mice and rats are ongoing Thalidomide was negative in tests for mutagenicity in *Salmonella typhimurium, Escherichia coli* and Chinese hamster ovary cells *in vitro*, and did not induce micronuclei in the bone marrow of mice

Use in pregnancy – (Category X)

Thalidomide is a known human teratogen and should not, under any circumstances, be administered during pregnancy, or to women of child-bearing potential, unless they are using two effective means of contraception. A single dose taken by pregnant women can cause birth defects Thalidomide has been found in the semen of men taking the drug, therefore thalidomide should not be taken by pregnant women or by their heterosexual partners

Male patients should use adequate contraceptive methods

If a female patient, or female partner of a male patient misses, or is suspected to have missed her period or there is any abnormality in menstrual bleeding, or suspects she is pregnant then a pregnancy test and counselling should be performed

If pregnancy occurs in a patient during thalidomide treatment, thalidomide should be discontinued immediately

The patient or pregnant partner should be referred to an obstetrician or gynaecologist experienced in reproductive toxicity for further evaluation and counselling

Use in lactation

It is not known whether thalidomide is excreted in human milk Women who are taking thalidomide should not breast feed

Effects on ability to drive and use machines

Thalidomide may cause sedation, drowsiness, somnolence and orthostatic hypotension If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks while being treated with Thalidomide Pharmion 50mg Hard Capsules

ADVERSE REACTIONS:-

The most commonly observed adverse reactions associated with the use of thalidomide are constipation, somnolence, asthenia

The other clinically most important adverse reactions associated with the use of thalidomide include sensory peripheral neuropathy, orthostatic hypotension, neutropenia, severe skin reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis, headache, rash, eosinophilia, peripheral oedema, dyspnoea,

dizziness, hypotension, bradycardia, symptomatic hypothyroidism, increase or decrease in platelet count, anaemia and, in HIV patients, an increase in HIV viral load

The following table contains frequencies for those adverse events for which a causal relationship with drug treatment could reasonably be established during investigational studies and post-marketing experience with the drug in the US Frequencies are defined as

very common ≥10%,

common ≥ 1%, <10%,

uncommon ≥0 1%, <1%,

rare ≥0 01%, <0 1%,

very rare <0 01%) including isolated reports

Blood and lymphatic system disorders:

Common	leukopenia, neutropenia
Very rare	eosinophilia, thrombocytopenia, anaemia

Metabolism and nutrition disorders:

Rare	increased appetite

Endocrine disorders:

Very rare	hypothyroidism

Psychiatric disorders:

Common	mood changes
Very rare	libido decreased, confusion

Nervous system disorders:

Very common	somnolence peripheral sensory neuropathy
Common	drowsiness, dizziness, paraesthesia, headache
Uncommon	tremor
Very rare	seizures

Cardiac disorders.

Rare	bradycardia, tachycardia, cardiac arrhythmia

Vascular disorders.

Rare	deep vein thrombosis
Very rare	orthostatic hypotension, thrombo-embolic events

Respiratory, thoracic and mediastinal disorders:

Uncommon	dyspnoea
Very rare	bronchospasm

Gastro-intestinal disorders:

Common	constipation, nausea, dry mouth
Very rare	intestinal obstruction

Skin and subcutaneous system disorders:

Common	rash, urticaria
Very rare	pruritus, serious bullous skin reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis, dry skin, facial oedema, photosensitivity

Reproductive system and breast disorders

Very rare	'menstruation abnormalities'

General disorders and administration site disorders:

Common	asthenia, peripheral oedema, weakness, fatigue, lethargy
Rare	malaise

Teratogenicity (see Precautions):

The most serious toxicity associated with thalidomide is teratogenicity The risk of severe birth defects, primarily phocomelia or death to the foetus, is extremely high during the critical period of pregnancy The critical period is estimated to range from 35 to 50 days after the last menstrual period The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant Thalidomide must not be used at any time during pregnancy

Neurological adverse events, especially somnolence and peripheral sensory neuropathy, were very common Monitoring during thalidomide treatment should include regular SNAP assessments

DOSAGE AND ADMINISTRATION:-

Multiple myeloma (adult dosage):

Dosing should be initiated at 200mg daily orally and increased by 100mg at weekly intervals to a maximum dose of 800mg daily according to tolerance and toxicity Depending on tolerance and observed toxicity, lower maintenance doses can be used

Erythema Nodosum Leprosum (adult dosage):

Dosing should be initiated at 100mg daily orally and, only where symptoms remain uncontrolled, increased by 100mg at weekly intervals according to tolerance and toxicity (see Clinical Trials section for results of Study E-003P) The maximum recommended dose is 400mg daily Depending on tolerance and observed toxicity, lower maintenance doses can be used than those used to control the active reaction

In patients with moderate to severe neuritis (due to leprosy) or other serious complications (e g uve tis), corticosteroids and other appropriate therapy may be started concomitantly and tapered/discontinued when neuritis etc has improved

There have been no well-controlled studies of thalidomide as maintenance therapy to prevent ENL relapse to provide maintenance dosing recommendations In study E-003P only 1 of 23 patients was tapered from treatment successfully using a 3-7 week tapering regimen Given the risks associated with ongoing thalidomide treatment, it is suggested that tapering (with the aim of discontinuation) be attempted every 3-6 months, in decrements of 50mg every 2 to 4 weeks

To reduce central nervous system effects (e g drowsiness, somnolence, sedation) during the day, this dose is normally taken as a single dose in the evening Thalidomide Pharmion 50mg Hard Capsules should be taken at least one hour after food

Storage

Store below 25°C Store in the original package in order to protect from light

OVERDOSAGE

Three cases of overdose have been reported concerning doses up to 14 4g No fatalities have been reported and all overdose patients recovered without sequelae

PRESENTATION:-

Each white opaque capsule contains 50mg thalidomide and is marked "Thalidomide 50mg Pharmion" with a "Do not get pregnant" symbol

Excipients anhydrous lactose, microcrystalline cellulose, crospovidone, povidone, stearic acid, colloidal anhydrous silica The capsule shells contain gelatin and titanium dioxide (E171) The printing ink is composed of shellac and black iron oxide (C177499)

Packaging consists of PVC/PE/Aclar blister (sealed with vinyl coated aluminium foil) of 14 capsules The blisters are further enclosed in boxes containing 2 blister strips to give a pack size of 28 capsules

POISON SCHEDULES:- S4

SPONSOR:-

Pharmion Pty Ltd

Level 1,476 St Kilda Road, Melbourne Vic 3004

AUST R No: 96672

Date of TGA Approval of Product Information:- October 7th 2003

Pharmion Pty Ltd
Level 1, 476 St Kilda Road, Melbourne 3004

PHARMION

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